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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/590,508	11/30/2006	Anthony John Freemont	69494-003US0	6795

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EXAMINER	
SGAGIAS, MAGDALENE K	

ART UNIT	PAPER NUMBER
1632	

NOTIFICATION DATE	DELIVERY MODE
06/24/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/590,508	FREEMONT ET AL.	
	Examiner	Art Unit	
	Magdalene K. Sgagias	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 March 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-42* is/are pending in the application.

4a) Of the above claim(s) *1-22 and 24-37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23 and 38-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 August 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's arguments filed 03/29/2010 have been fully considered. The amendment has been entered. Claims 1-42 are pending. Claims 1-22, 24-37 are withdrawn.

Claims 23, 38-42 are under consideration.

The declaration of Dr Stephen Richardson pursuant to 37 CFR 1.132 has been considered.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of claims 23, 38-42 under 35 U.S.C. 103(a) as being unpatentable over Sanchez-Ramos et al, (Experimental Neurology, 164: 247-256, 2000) in view of Hutton et al, (Clinical Biomechanics, 16: 728-734, 2001 (IDS)); Hutton et al (Spine, 24(15): 1507-1515, 1999 (IDS)); Richardson et al, (European Cells and Materials, 6:Suppl. 2, 20, 2003) is withdrawn in view of the declaration.

Claims 23, 38-42 are rejected under 35 U.S.C. 103(a) are rejected as being unpatentable over **Sanchez-Ramos et al,** (Experimental Neurology, 164: 247-256, 2000 (IDS)) in view of **Risbud et al** [International Society for the Study of the Lumbar Spine, 30th annual meeting, (2003) Abstract #26 (IDS)]; **Le Visage** (International Society for the Study of the

Lumbar Spine, 30th annual meeting, (2003) Abstract #25); **Hutton et al,** (Clinical Biomechanics, 16: 728-734, 2001 (IDS)); **Gruber et al,** (Expert Opin Biol Ther, 3(8): 1209-1214, 2003 IDS)).

Sanchez-Ramos et al, teach exposing human bone marrow stromal mesechymal stem cells (MSSCs) to experimental culture conditions in the presence of EGF or BDNF the bone marrow stromal cells differentiate into neural cells in vitro (abstract). Sanchez-Ramos suggests understanding the molecular mechanisms responsible for neuronal differentiation of these cells will ultimately yield a readily available source of neural cells for cellular therapies ranging from gene therapeutics to neural reconstruction in neurodegenerative diseases, stroke, and trauma (p 255, 1st column). Sanchez-Ramos differs from the present invention for not teaching the MSSCs encapsulated in a gel to increasing pressures up to 30 psi and reduced oxygen pressure.

However, at the time the claimed invention was made, **Risbud et al** teaches MSC immobilized in 3-diemsional alginate gels and cultured in a hypoxic environment (2%) in medium supplemented with ascorbate and TGF-beta1 the MSCs respond to their microenvironment and begin to express a phenotype consistent with that of the exhibited by the cells of the nucleus pulposus (abstract #26). Risbud suggests said MSCs can be used to repopulate damaged or degenerate nucleus pulposus (abstract #26). Risbud does not teach exposing the alginated MSC and cultured in a hypoxic environment to increasing pressures of up to 30 psi (2.1 MPa).

This deficiency is cured by **Le Visage** (International Society for the Study of the Lumbar Spine, 30th annual meeting, (2003) Abstract #25). Le Visage teaches that there interaction between MSCs and intravertebral disc cells in culture in vitro associated with changes in the biosynthesis of extracellular matrix (abstract #25). **Hutton et al,** (Clinical Biomechanics, 16: 728-734, 2001 (IDS)) supplements the teachings of Le Visage by teaching IVD cells exposed to

specific values of hydrostatic pressure at 0.35 MPa and at atmospheric pressure (approximately 0.1 MPa) that hydrostatic pressure directly affects the synthesis of collagen and proteoglycan by the intervertebral disc cells (abstract). Hutton suggest that in life the higher the pressure (1MPa) would tend to cause a fluid egress from the IVD cells stimulates an increase in production of proteoglycans, these proteoglycans carry hydrophilic side chains, in other words, cells respond to higher pressure by producing more glycans, which have the capacity to resist fluid loss (p 733, 2nd column bridge to p 734). Hutton however, differ from the present invention for not teaching the affects of hydrostatic pressure on the secretion of collage synthesis and proteoglycan by MSSCs.

Gruber et al, (Expert Opin Biol Ther, 3(8): 1209-1214, 2003) who teaches co-culture of MSCs with nucleus cells there is an increase in the production of proteogycan (p 1211, 2nd column 4th paragraph) and when alginated MSCs implanted into degenerate disc site cells in vivo the MSCs may have differentiated into disc cells which then acted to preserve the annular structure and proteoglycan content (p 1212, 1st column).

The combination of prior art cited above in all rejections under 35 U.S.C. 103 satisfies the factual inquiries as set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966). Once this has been accomplished the holdings in KSR can be applied (*KSR International Co. v. Teleflex Inc. (KSR)*, 550 U.S. ___, 82 USPQ2d 1385 (2007): "Exemplary rationales that may support a conclusion of obviousness include: (A) Combining prior art elements according to known methods to yield predictable results; (B) Simple substitution of one known element for another to obtain predictable results; (C) Use of known technique to improve similar devices (methods, or products) in the same way; (D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results; (E) "Obvious to try" – choosing from a finite number of identified, predictable solutions, with a

reasonable expectation of success; (F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art; (G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention."

Accordingly, it would have been obvious to the ordinarily skilled artisan to modify the teachings of Sanchez-Ramos to utilizing alginated MSCs and cultured in a hypoxic environment, such as that taught by Risbud, with a reasonable expectation of success. One of ordinary skill in art would have been motivated to use alginate MSCs in order for the alginated MSCs to respond to their microenvironment and begin to express a phenotype as suggested by Risbud and in order to co-cultivate the alginated MSCs and increase the biosynthesis of proteoglycan matrix as suggested by Le Visage by using IVD cells exposed to hydrostatic pressure that hydrostatic pressure directly affects the synthesis of collagen and proteoglycan by the IVD cells as suggested by Hutton. Although Hutton discusses producing poteoglycan matrix synthesis by using hydrostatic pressure in the context of IVD cells, one of skill in the art would readily recognize that alginated MSCs would also be useful to use hydrostatic pressure, as noted by Hutton in order for the MSCs to increase proteoglycan biosynthesis. This is further underscored by the teachings of Le Visage who teaches that there is interaction between MSCs and intravertebral disc cells in culture associated with changes in the biosynthesis of extracellular matrix and particularly since Gruber teaches co-culture of MSCs with nucleus cells there is an increase in the production of proteogycan and when alginated MSCs implanted into degenerate disc site cells in vivo the MSCs may have differentiated into disc cells which then acted to preserve the annular structure and proteoglycan content (p 1212, 1st column). In addition, it is

evident that the person of ordinary skill would have optimized the oxygen pressure as a matter of design choice with reasonable expectation of achieving predictable results in human cells. One of ordinary skill in the art would have been sufficiently aware of these routine oxygen pressure optimization processes and would have used increments of oxygen pressure so as to include the instantly claimed increments in a human MSSC system in view of disclosure by both Hutton (2001). One who would practice the invention would have had reasonable expectation of success given that prior art teaches all the elements for causing human MSSCs to differentiate towards IVD cells it would have only required routine experimentation to apply to the MSSCs of Sanchez-Ramos encapsulated in a gel increasing pressures of up to 2.1 MPa and reduced increments of oxygen tension as taught by the combined cited references without undue experimentation.

The MPEP states that "A. Optimization Within Prior Art Conditions or Through Routine Experimentation Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be prima facie obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.); see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); In re Hoeschele, 406 F.2d

1403, 160 USPQ 809 (CCPA 1969) (Claimed elastomeric polyurethanes which fell within the broad scope of the references were held to be unpatentable there over because, among other reasons, there was no evidence of the criticality of the claimed ranges of molecular weight or molar proportions.). For more recent cases applying this principle, see Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); In re Kulling, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997).

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Applicant's arguments are rebutted as they are relevant to the new rejection.

Applicants argue that Hutton reference teaches applying the hydrostatic pressure on IVD cells and not on MSC. These arguments are not persuasive because the co-culture system of alginated MSCs with IVD cells and the interactions between the MSCs and IVD cells in the context of increasing proteoglycan matrix biosynthesis increased by applying hydrostatic pressure as discussed above. As discussed above based on the combined references it would have been obvious for an ordinary of skill in the art to apply hydrostatic pressure in MSCs for causing human MSSCs to differentiate towards IVD cells since Gruber teaches co-culture of MSCs with nucleus cells there is an increase in the production of proteogycan and when alginated MSCs implanted into degenerate disc site cells in vivo the MSCs may have differentiated into disc cells which then acted to preserve the annular structure and proteoglycan content. In addition, it would have only required routine experimentation to apply to the MSSCs of Sanchez-Ramos encapsulated in a gel increasing pressures of up to 2.1 MPa and reduced increments of oxygen tension as taught by the combined cited references without undue experimentation.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene K. Sgagias whose telephone number is (571)272-3305. The examiner can normally be reached on Monday through Friday from 9 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paras Peter can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Art Un it 1632

/Anne-Marie Falk/
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